IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PURDUE PHARMA PRODUCTS L.P., NAPP PHARMACEUTICAL GROUP LTD., BIOVAIL LABORATORIES INTERNATIONAL, SRL, and ORTHO-MCNEIL, INC.,	)	Civil Action No. 07-255-KAJ (CONSOLIDATED)
Plaintiffs/Counterclaim-defendants,	)	
v.	)	
PAR PHARMACEUTICAL, INC., and PAR PHARMACEUTICAL COMPANIES, INC.,	)	
Defendants/Counterclaim-plaintiffs.	)	

MEMORANDUM OPINION

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JORDAN, *Circuit Judge*.[1]

I. INTRODUCTION

Plaintiffs Purdue Pharma Products L.P. ("Purdue"); Napp Pharmaceutical Group LTD. ("Napp"); Biovail Laboratories International, SRL ("Biovail");[2] and Ortho-McNeil, Inc. ("Ortho-McNeil") filed this patent infringement action against Defendants Par Pharmaceutical, Inc. ("Par Pharmaceutical") and Par Pharmaceutical Companies, Inc. ("Par Pharmaceutical Companies") under the Hatch-Waxman Act, 35 U.S.C. § 271(e). The Complaint[3] is based on Par Pharmaceutical's submission of an Abbreviated New Drug Application ("ANDA") to the United States Food and Drug Administration ("FDA"). (D.I. 78 at 3 ¶ 12; D.I. 98 at 7 ¶ 15.) With the ANDA, Defendants seek FDA

[1]Sitting by designation (Docket Item ["D.I."] 241).

[2]The parties indicate that Biovail soon may be voluntarily dismissed from this case. (D.I. 259.)

[3]For ease of reference, Plaintiffs' Amended Complaint (D.I. 78) is referred to herein as the "Complaint."

approval to manufacture and market extended release tablets containing a generic version of the analgesic known as "tramadol." (D.I. 78 at 3 ¶ 12; D.I. 98 at 3 ¶ 12.) At issue in this case is whether the ANDA submission infringes U.S. Patent No. 6,254,887 (the "'887 patent"), whether the tablets described in the ANDA would, if manufactured and marketed, infringe U.S. Patent No. 7,074,430 (the "'430 patent"), and whether those patents are valid and enforceable.

Before me are the parties' requests that I construe the disputed claim language of the '887 and '430 patents. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967 (Fed. Cir. 1995) (en banc), *aff'd* 517 U.S. 370 (1996). The parties have fully briefed and argued their positions. Jurisdiction is proper under 28 U.S.C. §§ 1331 and 1338.

II. BACKGROUND

A. The Parties

Plaintiffs Purdue and Napp are owners by assignment of the '887 and '430 patents. (D.I. 78 at 1-2.) Biovail is the holder of New Drug Application ("NDA") No. 21-692 and manufactures the controlled release tramadol pain relief medication ULTRAM ® ER.[4] (*Id.* at 2 ¶ 6.) Ortho-McNeil is a licensee of the '887 patent and markets and distributes ULTRAM ® ER in the United States. (*Id.* at 2 ¶ 7.)

[4]ULTRAM ® ER contains a salt of tramadol, specifically tramadol hydrochloride. (*Id.* at 2 ¶ 6; D.I. 161 at 4; D.I. 222, Exh. 3 at 7.)

Based on the parties' submissions, the division of labor between the Par entities is unclear. Suffice it to say that Par Pharmaceutical is a wholly-owned subsidiary of Par Pharmaceutical Companies (*Id.*; D.I. 98 at 2-3), and it appears as though the Par entities are in the business of developing, manufacturing, and marketing generic versions of FDA-approved pharmaceuticals.

B. The Disclosed Technology

The application for the '887 patent was filed on July 10, 1996 as a divisional of U.S. Patent No. 5,591,452 (the "'452 patent").[5] The '887 patent is directed to "a controlled release preparation comprising tramadol or a pharmaceutically acceptable salt thereof." ('887 patent at 1:8-9.) It has as an object "to provide an oral controlled release tramadol preparation suitable for at least twelve-hourly (e.g. up to twenty-four hourly) administration for pain." (*Id.* at 1:22-25.) Tramadol "is an orally active opioid analgesic ... [that has] been commercially available for many years for use in the treatment of moderate to severe pain." (*Id.* at 1:10-18.)

[5]A "divisional" application is one carved out of an earlier application which disclosed and claimed more than one independent invention, the result being that the divisional application claims only one or more, but not all, of the independent inventions of the earlier application. *Transco Prods. Inc. v. Performance Contracting Group, Inc.*, 38 F.3d 551, 555 (Fed. Cir. 1994) (citing The Manual of Patent Examining Procedure (MPEP) § 201.06 (1988)).

The specification discloses the following figure comparing the plasma profile, in five healthy male volunteers, resulting from a single dose of controlled release tramadol ("OD Tablet 200mg") to immediate-release tramadol ("Tramal drops 100 mg"):

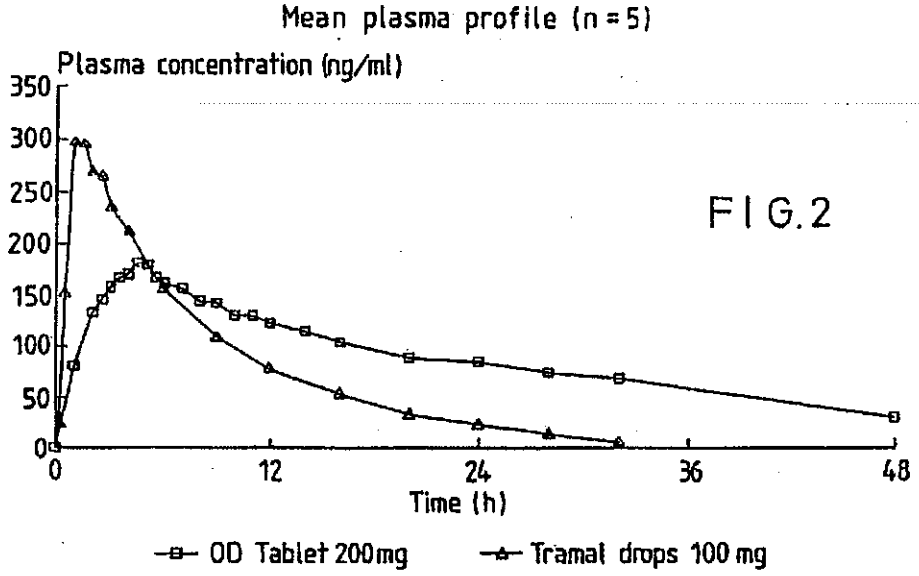

FIG.2

(*Id.* at Fig. 2, 12:11-14.)

Plaintiffs claim that the submission of Defendants' ANDA infringed claims 1, 3, 13, 15, 16, 19, 23, 27, 29 and 31 of the '887 patent. (D.I. 157 at 9.) All of the asserted claims either depend from or are closely related to claim 1. It reads as follows:

> A controlled release oral pharmaceutical preparation suitable for dosing every 24 hours comprising
>
> a substrate comprising a pharmaceutically effective amount of tramadol or a salt thereof;
>
> said substrate coated with a controlled release coating;
>
> said preparation having a dissolution rate in vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0,1 N hydrochloric acid at 37° C. and using UV detection at 270 nm,

> between 0 and 50% tramadol released after 1 hour; between 0 and 75% tramadol released after 2 hours; between 3 and 95% tramadol released after 4 hours; between 10 and 100% tramadol released after 8 hours; between 20 and 100% tramadol released after 12 hours; between 30 and 100% tramadol released after 16 hours; between 50 and 100% tramadol released after 24 hours; and greater than 80% tramadol released after 36 hours, by weight, said preparation providing a therapeutic effect for about 24 hours after oral administration.

('887 patent at 12:16-34.)

The application for the '430 patent was filed on March 6, 2001 and is a continuation of the application that became the '887 patent.[6] Plaintiffs assert that the tablet described in Defendants' ANDA would infringe claims 1, 3, 5, 6, 7, 11, 12, 13, 14, and 15 of the '430 patent. (D.I. 157 at 9.) Claim 1 is the only independent claim in the '430 patent. It reads as follows:

> A solid controlled release oral dosage form, comprising,
> a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof incorporated into a normal release matrix,
> said matrix overcoated with a controlled release coating comprising a polymethacrylate or a water insoluble cellulose,

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[6] A "continuation" application claims the same invention claimed in an earlier application, although there may be some variation in the scope of the subject matter claimed. *Transco Prods.*, 38 F.3d at 555 (citing MPEP § 201.07). Both a divisonal and a continuation application share the same disclosure as the original application. *Id.* The '430 specification incorrectly states that the '887 patent application was filed as a continuation of the application that became the '452 patent. The file history for the '887 patent confirms that its application was filed as a divisional, rather than a continuation, of the application that became the '452 patent. (D.I. 163, Exh. C at PAR046152.)

said dosage form providing a therapeutic effect for at least about 24 hours.

('430 patent at 12:41-51.)

C. The Procedural History

In January 2007, Defendants submitted an ANDA seeking FDA approval to sell generic tramadol extended release tablets. (D.I. 161 at 4.) Pursuant to the Hatch-Waxman Act, 21 U.S.C. § 355(j)(iv), Defendants submitted information to show that its proposed generic tablet is bioequivalent to ULTRAM ® ER. (D.I. 161 at 4.) Because the FDA lists ULTRAM ® ER as covered by the '887 patent,[7] Defendants also certified that the '887 patent is invalid or will not be infringed by the manufacture, use, or sale of its generic tablets. (*Id.*; 21 U.S.C. § 355(j)(2)(A)(vii)(IV).)

Plaintiffs filed the current action on May 9, 2007. They allege that the submission of Defendants' ANDA infringed the '887 patent and they request a declaratory judgment that Defendants' tablets, if manufactured and marketed, would infringe the '430 patent. (D.I. 78.)

III. APPLICABLE LAW

The rules of claim construction are well known and need not be repeated here. It is sufficient to note that "the claims themselves provide substantial guidance as to the

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[7]For a description of the manner in which the FDA publishes information on drug products, see *Abbott Laboratories v. Teva Pharmaceuticals USA*, 432 F. Supp. 2d 408, 414-15 (D. Del. 2006).

meaning of particular terms" and that a patent's specification "is always highly relevant to the claim construction analysis." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314-15 (Fed Cir. 2005) (en banc) (citations omitted).

IV. CLAIM CONSTRUCTION

A. "therapeutic effect"

1. The Parties' Proposed Constructions

The parties appear to agree that the term "therapeutic effect" can be defined as "an effective treatment for pain." Defendants explicitly adopt this understanding by using the synonymic term "analgesic efficacy" in their proposed claim construction (D.I. 161 at 1) and defining "therapeutic effect" as "pain relief" in their briefing.[8] Plaintiffs, on the other hand, initially defined "therapeutic effect" as "effective for the treatment of one or more clinical conditions, e.g., pain," suggesting that "therapeutic effect" may apply to some condition other than pain. (D.I. 157 at 12.) At the *Markman* hearing, however, Plaintiffs conceded that the only clinical condition treated by the invention is pain (D.I. 249 at 45:15-20)[9] and defined "therapeutic effect" as "effective for the treatment of pain."

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[8] See, e.g., "Given that the pharmaceutical or therapeutic effect of tramadol is analgesia (pain relief)... ." (D.I 181 at 12.); "And the term 'therapeutic effect' as it relates to tramadol, a known analgesic agent, would be considered to mean that the product described by the claims causes an analgesic effect, which is 'reduced response to painful stimuli'... ." (D.I. 161 at 15 (quoting Weinberger Dec., ¶ 15).); "'[T]herapeutic effect for about 24 hours' as it relates to orally administered tramadol is assessed for a duration of 24 hours from the time that pain relief begins, i.e., onset of action." (D.I. 161 at 18.)

[9] D.I. 249 is the transcript of the *Markman* hearing.

(*Id.* at 45:4, 8-9.) Since Plaintiffs have adjusted their position, the parties share the understanding that "therapeutic effect" means "an effective treatment for pain."

The parties' remaining dispute regarding this term is whether the therapeutic effect must be "demonstrated by scientifically valid placebo-controlled clinical evidence." (D.I. 247 at 3.) Defendants argue that a person of ordinary skill in the art would expect a "therapeutic effect" to be shown by a scientifically valid study. (D.I. 181 at 3.) Such a study, Defendants maintain, would necessarily include controls to account for the placebo effect.[10] (*Id.*) In support of that position, Defendants rely on the opinions of their experts, Dr. Weinberger and Dr. Grond. (D.I. 161 at 16-17 (citing Weinberger Dec. ¶ 18-20, 23); D.I. 181 at 3-4 (citing Grond Dec., ¶ 23).) Dr. Grond bases his opinion, in part, on two scholarly articles[11] from the applicable time period. (D.I. 181 at 3-4 (citing Grond Dec., ¶ 23).)

Defendants also contend that the prosecution history of the '430 patent supports their position. (D.I. 161 at 12-13.) Specifically, Defendants contend that during the prosecution of the '430 patent, the patentees distinguished a prior art reference, European Patent No. 0147780 ("the Bondi reference"), by arguing that "there are no clinical trials

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[10] "A placebo effect is a change in a patient's illness attributable to the symbolic import of a treatment rather than a specific pharmacologic or physiological property." Turner, J.A. et al. (1994) "The Importance of Placebo Effects in Pain Treatment and Research," JAMA 271(20): 1609 ("Turner").

[11] Dr. Grond cites Turner, JAMA 271(20): 1608-1614 and Wall, P.D. (1993) "Pain and the placebo response," Ciba Foundation Symposium, 174:187-211.

reported therein, there are no indications that the dosage forms described therein were ever administered to human subjects, and there is no teaching or suggestion of any desired pharmacokinetic parameters ... ." (*Id.*) Defendants assert that this is an acknowledgment by the patentees that a claim of therapeutic effect must be demonstrated by scientifically valid clinical evidence. (D.I. 161 at 13.)

Plaintiffs argue that it would be improper to accept Defendants' proposed limitation because it is not supported by the intrinsic evidence. (D.I. 157 at 14 (citing *Burke, Inc. v. Bruno Indep. Living Aids, Inc.*, 183 F.3d 1334, 1340-41 (Fed. Cir. 1999)).) They also contend that, in distinguishing the Bondi reference, the patentees did not specify how therapeutic effect is to be proven. (D.I. 178 at 5.) Rather, they simply listed clinical trials and pharmacokinetic parameters as alternative approaches that could be used to prove therapeutic effect. (*Id.*) Thus, Plaintiffs stress that pharmacokinetic parameters can be established in clinical testing that does not involve controls for the placebo effect. (*Id.* (citing Smith Dec., ¶ 7 and Davies Dec., ¶¶ 31-32).)

2. The Court's Construction

The intrinsic evidence does not support a limitation that therapeutic effect must be demonstrated by scientifically valid placebo-controlled clinical evidence. Neither the claims nor the specifications mention placebo-controlled clinical evidence or imply that it is necessary to prove therapeutic effect. To the contrary, the specification reveals that the

therapeutic effect of tramadol is already accepted in the art,[12] stating that it has been "commercially available for many years for use in the treatment of moderate to severe pain." ('887 patent at 1:15-17.) In addition, the portion of the prosecution history cited by Defendants militates against, rather than for, such a limitation. It indicates that the inventors believed that tramadol's therapeutic effect for a 12- or 24-hour period could be proved using pharmacokinetic parameters, which can be measured in clinical trials that do not control for the placebo effect. In short, there is no support in the intrinsic evidence for adding Defendants' proposed limitation, and I decline to do so. Accordingly, I will construe the term "therapeutic effect" to mean "an effective treatment for pain."

B. "A [solid] controlled release oral [dosage form/pharmaceutical preparation/pharmaceutical tablet] ... said [dosage form/pharmaceutical preparation/pharmaceutical tablet] providing a therapeutic effect for [at least] about 24 hours"

1. The Parties' Proposed Constructions

The parties' dispute over this term is focused on the type of dosing environment the claims require to determine whether there is a therapeutic effect for about or at least

[12]Plaintiffs suggest that the qualifications of a person having ordinary skill in the art would be one with experience as a formulator (one who makes a drug), a pharmacokineticist (one who researches and characterizes the drug), and a clinician (one with experience in treating pain). (D.I. 249 at 13:14-16:1.) Defendants would not include a pharmacokineticist in their list of qualifications. (*Id.*) However, a number of the claims, such as claim 16 of the '887 patent, refer to pharmacokinetic paramaters. I therefore believe that the Plaintiffs' suggestion better captures what a person of skill in the art would need to know in order to practice the invention, and I will adopt it.

about 24 hours.[13] Plaintiffs contend that it is common to characterize controlled release formulations in terms of their performance at "steady state," or the point where the absorption and elimination of a drug are such that each successive dose provides a predictable blood plasma level. (D.I. 221, Exh. A at 7 (citing *Purdue Pharma L.P. v. Boehringer Ingelheim GmbH*, 98 F. Supp. 2d 362, 374-76 (S.D.N.Y. 2000)).) While disclaiming any intent to insert a steady state requirement into the claims, Plaintiffs argue that the claims necessarily imply that a patient will take repeated doses and that a person skilled in the art would understand that a first dose would not immediately produce pain relief. (*Id.*) Plaintiffs thus propose that the claims should be understood to mean that "the 24-hour therapeutic effect can be measured in an environment of repeated dosing, and is not limited to the therapeutic effect of any single tablet." (D.I. 247 at 7.)

Defendants argue that the 24-hour therapeutic effect must be measured with a single dose, taken in isolation. Specifically, Defendants propose the following construction:

> The dosage form [pharmaceutical preparation, or coated tablet] provides a therapeutic effect for about [or at least about] 24 hours. The therapeutic effect shall be provided by the specific dosage form, [pharmaceutical preparation, or coated tablet] in question, not provided by other sources, including additional or previously administered dosage forms [pharmaceutical preparations, or coated tablets].

(*Id.*)

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[13]The "at least" addition to the phrase "about 24 hours" is a feature of claim 1 of the '430 patent.

Both sides argue that the claim language is in their favor. Plaintiffs rely on the rule of claim construction, applicable to both patents, that the word "a" in a claim with the term "comprising" means "one or more." *See Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1342 (Fed. Cir. 2008). Thus, Plaintiffs argue that the term "a solid controlled release oral dosage form" means that one or more solid controlled release oral dosage forms may be used to achieve a 24-hour therapeutic effect.[14] (D.I. 249 at 22:20-23:6.) Plaintiffs also assert that the "suitable for dosing every 24 hours" language in the independent claims of the '887 patent supports their argument that the claimed formulation is intended for multiple dosing. (D.I. 221, Exh. A at 8.)

Defendants respond that the word "a" should not be understood to mean "one or more" because it is used in the preamble rather than after the word "comprising." In this context, Defendants argue that "a" means only one. (D.I. 249 at 36:7-22.) Defendants also argue that the phrase "said dosage form providing a therapeutic effect for at least about 24 hours" makes clear that the 24-hour therapeutic effect is a property of the claimed dosage form, not a result achieved from a sequential dosing regimen. (D.I. 205, Exh. A at 6.) Defendants warn that Plaintiffs are trying to transform a product claim into

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[14]While claim 1 claims a "pharmaceutical preparation," independent claim 13 claims a "pharmaceutical tablet" and claim 1 of the '430 patent claims a "dosage form." For purposes of claim construction, both sides conceded at oral argument that "pharmaceutical preparation," "pharmaceutical tablet," and "dosage form" have the same meaning, namely a tablet. (D.I. 249 at 37:20-38:16.) I will therefore use these terms interchangeably.

a method claim for the treatment of pain. (*Id.*) Finally, as to the claim language, Defendants contend that because some of the dependent claims refer to certain pharmacokinetic parameters, and because those parameters measure properties of a single tablet, therapeutic effect must also be measured by the response to a single tablet.[15]

Both sides attach meaning to the specification's silence as to a dosing regimen. Plaintiffs argue that it was unnecessary to detail a multiple-dosing regimen in the specification because the fundamental purpose of the invention, as set forth in the title of both the '887 and '430 patents, is to provide a controlled release tramadol formulation, and the purpose of controlled release formulations generally, as understood by those with skill in the art, is to treat patients who require repeated dosing for an extended period of time. (D.I. 221, Exh. A at 11.) Plaintiffs look to Biovail's package insert for ULTRAM® ER as support for the argument that it is common to characterize controlled release formulations in terms of their steady state performance. (D.I. 221, Exh. A at 7.) In particular, the insert explicitly provides performance statistics at steady state (D.I. 222, Exh. 7 at PUR1015268) and indicates that ULTRAM® ER is to be used for "the management of moderate to moderately severe *chronic* pain in adults who require around-

[15]For example, dependent claim 11 of the '887 patent refers to "W_{50}." The parties agree that W_{50} means "[t]he width of the plasma profile at 50% C_{max}, *i.e.*, the duration over which the plasma concentrations are equal to or greater than 50% of the peak concentration." (D.I. 247 at 10.) Plaintiffs acknowledge that W_{50} is measured over a single dosing interval, but contend that it need not be measured with a single pill taken in isolation. (D.I. 249 at 26:11 - 28:9.)

the-clock treatment of their pain for an *extended period of time*." (*Id.* at PUR1015269 (emphasis added).)

Defendants contended at oral argument that a person of ordinary skill in the art would not understand "controlled release" to imply multiple doses. They argued that extended release medications may be prescribed for acute pain, such as for providing 24-hour pain relief following a surgery. (D.I. 249 at 32:16-22.) Defendants included in one of their expert reports a study that Biovail conducted in 2000 to measure the efficacy of tramadol HCl extended release tablets[16] when used to prevent acute dental pain following molar extractions. (Weinberger Expert Rep., Ex. 17 at BVF00274354.) Moreover, Defendants emphasize that the only data on drug efficacy provided in the shared specification of the '887 and '430 patents was measured following the administration of a single dose.[17] (D.I. 205, Exh. A at 8-9.)

2. The Court's Construction

As a preliminary matter, I am persuaded that a person of ordinary skill would understand the term "controlled release" as it is used in the patents-in-suit to describe the

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[16]Plaintiffs allege, and Defendants do not appear to seriously dispute, that "extended release" – a term that does not appear in the patent claims but does appear in the FDA submissions of both Biovail and Defendants – and "controlled release" have identical meanings. (D.I. 222, Ex. 7 at 6.)

[17]*See* '887 patent at 8:51-53 ("In a trial involving 12 healthy volunteers the serum levels of tramadol following *administration of one tablet* according to Example 2 was found to be as illustrated in FIG. 1." (emphasis added)); 12:11-14 ("In a trial involving five healthy male volunteers the plasma profile resulting from *single dose administrations* of the above tablet are shown in FIG. 2." (emphasis added)).

composition of an individual pill. I cannot conclude that one of skill in the art would understand the term so expansively as to also encompass a repeated-dosing environment within which the efficacy of the pill is tested. As Plaintiffs acknowledged at oral argument, the inventors disclosed in the specification the data for controlled release tramadol that they had available at the time they filed the '452 patent, the parent of the patents-in-suit. (D.I. 249 at 54:20-24.) That data related to a single-dose environment only, yet it did not prevent the inventors from calling their invention a "controlled release" formulation. Even absent Plaintiffs' concession, the specification defines a "controlled release preparation" without reference to multiple doses: "A controlled release preparation according to the present invention is one that achieves slow release of a drug over an extended period of time, thereby extending the duration of drug action over that achieved by conventional delivery." '887 patent at 1:34-37. This definition must control. *Phillips*, 415 F.3d at 1316.[18]

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[18]The contents of the ULTRAM® ER package insert do not alter my opinion. Biovail, a company that is not now and has never been an assignee of the patents-in-suit, submitted its NDA for ULTRAM® ER in December of 2003, approximately nine years after the '452 patent was filed and over two years after the filing of the '430 patent. (Perkins Expert Rep., Ex. 5 at SBA000040.) Even if I were inclined to go in search of extrinsic evidence, this later-developed information regarding a product that Plaintiffs claim to be covered by the patents-in-suit provides little insight into what the patent claims meant at the time they were filed. *See PC Connector Solutions LLC v. SmartDisk Corp.*, 406 F.3d 1359, 1363 (Fed. Cir. 2005) ("[A claim's] meaning must be interpreted as of its effective filing date.").

Recognizing this definition of "controlled release preparation," however, does not end the inquiry as to whether the term in controversy constricts the type of dosing environment used to measure therapeutic effect. To decide that issue, the entirety of the claim must be examined in light of the specification. *Phillips*, 415 F.3d at 1315.

I conclude that the independent claims require that one tablet provide the claimed therapeutic effect. Defendants are correct that the general rule defining "a" to mean "one or more" does not apply here, so there is no basis for Plaintiffs' presumption that the claims cover a repeated-dosing environment. Traditionally, "a" means "one or more" in "comprising" claims because "comprising" is an open transition phrase. *Scanner Techs. Corp. v. ICOS Vision Sys. Corp., N.V.*, 365 F.3d 1299, 1305-06 (Fed. Cir. 2004). "When a claim uses an 'open' transition phrase, its scope may cover devices that employ additional, unrecited elements." *AFG Indus., Inc. v. Cardinal IG Co., Inc.*, 239 F.3d 1239, 1244 (Fed. Cir. 2001). The decision in *Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338 (Fed. Cir. 2008), provides a good example of how the "one or more" rule should apply. The claim at issue read: "A pre-packaged, pre-soaked cleaning system ... comprising in combination: (1) a pre-soaked fabric roll ... said fabric roll having a sealed sleeve ... ." 512 F.3d at 1340. The Federal Circuit held that, absent anything in the record indicating a contrary meaning, "a pre-soaked fabric roll" was not limited to a single roll. *Id.* at 1343. Thus, the invention in *Baldwin Graphic*, a pre-packaged, pre-soaked cleaning system, could contain more than one pre-soaked fabric roll. Similarly, applying the rule

to the '887 patent might mean, for example, that a single tablet could contain something in addition to "a substrate" and "a controlled release coating" (including, for example, additional substrates or controlled release coatings). It does not mean, however, that additional tablets, the very invention that the claims define, can be used to achieve the required therapeutic effect.

Plaintiffs argue that because the phrase "said preparation" occurs after "comprising" the *Baldwin Graphic* rule nonetheless applies. But *Baldwin Graphic* itself warned, albeit in a scenario where the antecedent phrase could carry a plural meaning, that the use of a definite article ("said") to refer to an antecedent phrase did not change the numerosity of the antecedent phrase. *Id.* at 1343. Thus, the use of the anaphoric phrase "said preparation" following "comprising" does not change the singular nature of the antecedent phrase "a controlled release oral pharmaceutical preparation."[19]

Nothing else in the claims or the remaining intrinsic evidence leads me to a different conclusion. Plaintiffs' reliance on the "suitable for dosing every 24 hours" language is not persuasive. This limitation is not in the '430 patent, and Plaintiffs acknowledged at oral argument that the differences in claim language between the

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[19]Although a term in the preamble does not generally limit the claimed invention, that rule does not apply where, as here, the preamble provides an antecedent basis for "said preparation." *See Rapoport v. Dement*, 254 F.3d 1053, 1059 (Fed. Cir. 2001) ("[W]ithout treating the phrase 'treatment of sleep apneas' as a claim limitation, the phrase 'to a patient in need of such treatment' would not have a proper antecedent basis.").

patents, on this point at least, are irrelevant. (D.I. 249 at 20:14-15.) Because both parties agree that construction of this term should be the same for both patents-in-suit, I am unable to conclude that language missing from one of the patents dictates the dosing environment for both. But even if the language were in both patents, I agree with Defendants that a person of skill, reading the claim language at issue, would have no reason to link a drug's dosing regimen to the therapeutic effect provided by a single dose. (D.I. 162 at 9 ¶ 23.)

Indeed, the specification indicates that the dosing regimen provided in the claims relates not to a repetition of doses over several days to achieve a therapeutic effect but to the amount of tramadol released from one or two tablets during about 24 hours. The specification provides five tables that list different *in vitro* release rates in terms of the percentage of tramadol released over time.[20] ('887 patent at 1:41-2:50.) For each hour listed, each table provides a range of percentage of tramadol released. The release rates in Table 2 are suited for twice-a-day dosing and so are of less relevance to the meaning of "suitable for dosing every 24 hours." (*Id.* at 1:58-2:8.) However, the other four tables are either unaccompanied by a dosing regimen (Table 1) or suggest that the given release rates are suited for once-a-day dosing (Tables 3-5).

Table 1 reads as follows:

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[20]Testing *in vitro* involves evaluating experimental formulations in fluids and under conditions that simulate to some extent the chemistry of the stomach and intestine. (D.I. 157 at 6.) Clinical testing in humans, in contrast, is called *in vivo* testing. (*Id.*)

TIME (H)	% RELEASED
1	0–50
2	0–75
4	3–95
8	10–100
12	20–100
16	30–100
24	50–100
36	>80

(*Id.* at 1:45-58.) According to this table, at hour 8, 10-100% of the tramadol from a single pill should be released.

Tables 3 and 4 list release rates that are "particularly suited for once-a-day dosings." (*Id.* at 2:9-38.) The entries for hour 8 in those tables list 35-100% and 10-65% tramadol released, respectively.

Table 5, reproduced below, lists release rates that are "more preferabl[e]" for once-a-day dosing.

TIME (H)	% TRAMADOL RELEASED
1	15–25
2	25–35
4	30–45
8	40–60
12	55–70
16	60–75

(*Id.* at 2:39-50.) The amount of tramadol released at hour 8 in that embodiment is between 40-60%.

These tables indicate that the narrower the range of release, the more preferable the preparation is for once-a-day dosing. The same narrowing of range is present for all

the corresponding hours as the tables move from preparations that are less suitable for once-a-day dosing to preparations that are more suitable.[21]

Though not presented in the briefing by either side, it appears that the narrower release ranges in once-a-day preparations may reflect a safety concern. (D.I. 249 at 40:4-9.) More specifically, it appears that, unless the amount of tramadol released is predictably controlled, a large percentage of tramadol might be released from a first pill after a second pill is taken, that is, after 24 hours following ingestion of the first pill. If a second pill were to release a large amount at the same time, it might introduce an unsafe level of tramadol in the bloodstream. Arguably, this indicates a consciousness on the part of the patentee that multiple doses may be needed in some cases, perhaps because of continuing or chronic pain. But safety and efficacy, though related, are not one and the same. That the concentration of tramadol provided by one pill needs to be controlled in a multiple-dosing regimen does not mean that the overall amount of tramadol released from one pill cannot provide a therapeutic effect over a 24-hour period. And it is to that therapeutic effect that the claims speak.[22]

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[21]Table 1 has the largest range of percentage tramadol released for each hour. Predictably, and entirely appropriately, claims 1 and 13 of the '887 patent claim this release rate, even though other tables list rates that are "suited for once-a-day dosing." By claiming a broad range of release rates, the claims still cover the narrower ranges found in the other tables.

[22]For the same reason, I decline to give the meaning Plaintiffs seek to the word "every" in the phrase "suitable for dosing every 24 hours." My understanding of "every 24 hours" is not that a tablet must be taken every 24 hours in order to achieve a

In sum, Plaintiffs' proposal would unduly broaden the patent claims. Nothing in the claims or the specification supports achieving the claimed therapeutic effect over the course of multiple doses. To the contrary, the claims list the elements of a single tablet, and every time the specification describes the results of administering controlled release tramadol to a human being it does so through the administration of a single tablet.[23] Accordingly, I will construe the term "A [solid] controlled release oral [dosage form/pharmaceutical preparation/pharmaceutical tablet] ... said [dosage form/pharmaceutical preparation/coated tablet] providing a therapeutic effect for [at least] about 24 hours" to mean "a single tablet, not including additional or previously administered tablets, that provides a therapeutic effect for [at least] about 24 hours."[24]

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therapeutic effect, but that tablets can effectively be used every 24 hours without safety concerns.

[23]Each side argues that its proposed construction is bolstered by an opinion in a separate patent infringement lawsuit brought by Purdue on an unrelated patent. *See Purdue Pharma L.P. v. Boehringer Ingelheim GmbH*, 98 F.Supp. 2d 362 (S.D.N.Y. 2000), *aff'd*, 237 F.3d 1359 (Fed. Cir. 2001). The claim at issue in *Boehringer* unambiguously stated that a certain pharmacokinetic parameter was to be measured "after repeated administration every 12 hours through steady-state conditions." 98 F.Supp. 2d at 369. The issue in *Boehringer* was whether a different claimed pharmacokinetic parameter was also to be measured in a repeated-dosing environment. *Id.* at 373. *Boehringer*, while being a thorough and thoughtful explanation of the issues before that court, does not help me resolve the present claim construction issue. To draw conclusions as to what lessons Purdue may have or should have gleaned from the prosecution of the patent in *Boehringer* or the subsequent litigation is too speculative an exercise. *See Medrad, Inc. v. MRI Devices Corp.*, 401 F.3d 1313, 1318 (Fed. Cir. 2005) (warning against basing construction on claim construction decisions from unrelated litigation).

[24]It is unnecessary to adopt Defendants' proposed construction to the extent it would include language guarding against measuring the therapeutic effect provided by

C. "therapeutic effect for about 24 hours after oral administration"

Having construed the term "therapeutic effect" I must still determine the meaning of the term "for about 24 hours after oral administration." The parties' dispute is over when the 24-hour period begins. This disagreement can be traced directly back to the parties' dispute over the dosing environment within which therapeutic effect is to be measured. For the reasons just set forth, I have decided that therapeutic effect is to be measured with a single pill. That construction effectively eliminates the parties' disagreement as to the meaning of "for about 24 hours after oral administration."

Defendants, who argued that therapeutic effect should be measured in a single-pill environment, have proposed a construction in which the 24-hour period begins at the onset of action. (D.I. 161 at 1.) Plaintiffs' counterargument that the 24-hour period is not linked to "when pain relief begins after the *first* dose" is predicated on measuring therapeutic effect in a repeated-dosing environment. (D.I. 157 at 21.) At the *Markman* hearing, however, Plaintiffs acknowledged that in a single-pill environment, therapeutic effect should be measured from when the treatment becomes effective. (D.I 249 at 46-47.) Plaintiffs also recognize in their briefing that there is a lag between when a single pill is administered and when it takes effect. (D.I. 221, Exh. A at 7.) Because both sides

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external sources such as a morphine drip. (D.I. 249 at 36:23-37:1.) Other than the numerosity of the tablet, Plaintiffs do not argue that something in addition to the tablet provides the required therapeutic effect, nor would that be a reasonable reading of the claims. As explained above, the claims themselves clearly dictate that it is the tablet alone that provides the contemplated therapeutic effect.

agree that the therapeutic effect provided by a single pill does not begin immediately, I will adopt a construction that starts the 24-hour period when the treatment begins to provide its intended effect.

At the *Markman* hearing, both parties opined that the phrase "after oral administration" does not add meaning to the term "therapeutic effect for about 24 hours after oral administration." Plaintiffs acknowledged that they view the phrase as irrelevant (D.I. 249 at 19), and Defendants agreed, stating that the phrase does not add meaning (D.I. 249 at 34). While I am hesitant to accept that a claim term does not add meaning, in this case I believe the parties are correct. The phrase "after oral administration" simply communicates that the treatment is to be taken orally and will not take effect until after it has been administered. The patent specification states repeatedly that the invention is to be taken orally and it is obvious that the treatment will not take effect until it has been administered. For the reasons stated above, I will construe the term "for about 24 hours after oral administration" to mean "for about 24 hours from when the treatment begins to provide its intended effect."

D. "therapeutic effect for at least about 24 hours"

This term is closely related to the term "therapeutic effect for about 24 hours after oral administration," which I construed above. The terms are so similar that Defendants have proposed that they be defined exactly the same way. (D.I. 161 at 17.) Plaintiffs recognize the addition of the words "at least" and include them in their proposed

construction. (D.I. 157 at 22.) The words "at least" have a plain meaning and in this context indicate that the effect of the treatment could last longer than about 24 hours. Accordingly, and for clarity, I will construe the term "therapeutic effect for at least about 24 hours" to mean "an effective treatment for pain for about 24 hours, or longer, from when the treatment begins to provide its intended effect."

E. "a pharmaceutically effective amount of tramadol or a salt thereof"

My construction of "therapeutic effect" largely resolves the parties' disagreement over the "pharmaceutically effective" term. Defendants propose that this term means "[a]n amount of tramadol or its salt contained in the substrate or the normal release matrix to achieve a therapeutic effect." (D.I. 247 at 4.) Plaintiffs object to Defendants' proposal insofar as it seeks to import the placebo-controlled clinical evidence requirement from its proposal for "therapeutic effect." (D.I. 249 at 86:3-20.) Since I have construed "therapeutic effect" so as not to require placebo-controlled clinical evidence – and I will not import that requirement into the "pharmaceutically effective" term for the same reasons[25] – Plaintiffs' objection falls away.

Defendants provide no intrinsic or extrinsic support for their proposed requirement that the tramadol be "contained in the substrate or the normal release matrix." Accordingly, I will construe "a pharmaceutically effective amount of tramadol or a salt

[25]Defendants acknowledge that "therapeutically effective," "pharmaceutically effective," and "analgesically effective" are synonyms. (D.I. 181 at 10 n.18.)

thereof" to mean "an amount of tramadol or its salt sufficient to achieve a therapeutic effect."

F. "matrix"

1. The Parties' Proposed Constructions

Plaintiffs propose that "matrix" means "A pharmaceutical preparation that incorporates the active ingredient dispersed within a solid dosage form." (D.I. 247 at 8.) Noting that claim 1 of the '430 patent, the only asserted claim that uses the term "matrix," uses the term only to refer back to the claim term "normal release matrix," and that the specification describes both "normal release" and "controlled release" matrices, Plaintiffs contend that the term "matrix" must be broad enough to encompass either a "controlled release matrix" or a "normal release matrix." Otherwise, Plaintiffs argue, the words "normal release" in the claim would be superfluous. (D.I. 157 at 15.)

Defendants maintain that the term "matrix" refers to a "system wherein a drug is incorporated into a polymer(s) structure by either particle or molecular dispersion, wherein the former is a suspension of drug particles homogenously distributed in the polymer(s) structure and in the latter drug molecules are dissolved in the polymer, and wherein drug release occurs by diffusion through and/or erosion of the polymer structure." (D.I. 161 at 19.) Defendants contend that their proposed construction is in fact broad enough to encompass both types of release matrices. The dispute over this

term thus largely boils down to whether Defendants are correct that their proposal is sufficiently broad.

Urging that the intrinsic record is not informative as to the meaning of the term "matrix," Defendants draw their construction from Yihong Qiu and Guohua Zhang, *Research and Development Aspects of Oral Controlled Release Technology*, 465, 466-67 (Donald L. Wise ed., 2000). Defendants argue that, as compared to Plaintiffs' construction, their construction offers needed clarity on the concept of "dispersion." (*Id.* at 20.)

Pointing to the testimony of their expert Dr. Martyn C. Davies, Plaintiffs contend that Defendants' construction describes only "controlled release" matrices because it allows for drug release only through "diffusion" or "erosion." (D.I. 157 at 16-17; D.I. 160 ¶ 34). Plaintiffs, like Defendants, resort mainly to the extrinsic record for their own construction, drawing their proposal from their expert's opinion. (D.I. 157 at 15.) To the extent Plaintiffs rely on the intrinsic record, it is only to criticize the fact that Defendants construction limits the term "matrix" to polymer-based structures. Along these lines, Plaintiffs note that the specification describes controlled release matrices incorporating waxes and vegetable oils, which Plaintiffs contend are not necessarily polymers. (*See id.* at 15; D.I. 249 at 69-70; D.I. 160 ¶ 35.) Thus, Plaintiffs argue, even if one assumes that Defendants' construction encompasses both "normal release" and "controlled release"

matrices, it is still wrong by virtue of its strictly limiting "controlled release" matrices to polymer-based structures.

2. The Court's Construction

I agree with the parties that the term "matrix" must be construed broadly enough to encompass both a "controlled release matrix" and a "normal release matrix." Turning first to Defendants' proposed construction, the article by Qiu and Zhang from which Defendants draw their construction (D.I. 170, Exh. S), and, in particular, the precise section from which Defendants draw their construction, is describing only a "controlled release matrix." Indeed, the article is entitled "Research and Development Aspects of Oral *Controlled-Release* Dosage Systems" and speaks on the topic of controlled release. (D.I. 170 Exh. S at 1 (emphasis added).) The precise section of the article from which Defendants ostensibly take their proposed construction is entitled "Common Oral Polymeric *Controlled-Release* Systems." (D.I. 170, Exh. S at 5 (emphasis added).) Further, the introductory sentence of the specific paragraph from which Defendants take their construction even explains that "[b]oth hydrophilic and hydrophobic polymeric matrix systems are widely used to provide *controlled delivery* of drug substances ... ." (*Id.* (emphasis added).) In light of this, it seems plain that the Qui and Zhang article, describing a system where drug release occurs by "diffusion and/or erosion," pertains to controlled release. (*Id.*) Moreover, the Qiu and Zhang article was published roughly seven years after the effective filing date of the patents-in-suit. It is not authored by any

of the inventors, and, while I do not doubt that the authors are respected scientists, there is no apparent reason for taking the article to be especially authoritative in the field. In these circumstances, I am, to put it mildly, wary of relying on this extrinsic evidence to limit the scope of a disputed claim term.

Likewise, I am reluctant to adopt a construction that limits the term "matrix" to polymer-based structures. Defendants contend that I should adopt this aspect of their construction because the patent describes both "controlled release" and "normal release" matrices as being polymer-based. (D.I. 181 at 8-9.) With respect to the structures the patent describes as making up "controlled release" matrices (*see* '887 patent at 3:48-67), Defendants contend that all of them would be understood by one of skill in the art to be polymers. (D.I. 181 at 9.) In support of that position, Defendants cite S. Venkatram et al., *An Overview of Controlled Release Systems*, 431, 443 (Donald L. Wise Ed. 2000), (D.I. 181 at 9 (citing D.I. 182, Ex. 1)), which, like the Qiu and Zhang article, was published roughly seven years after the effective filing date of the patents-in-suit, was not authored by any of the inventors, and does not appear unusually authoritative. I thus am not inclined to rely upon it to limit the scope of the claims.

Plaintiffs, pointing to the testimony of their expert, dispute the notion that the structures described in the patent as making up "controlled release" matrices are always polymers. For instance, Plaintiffs argue that "vegetable oils" are not always polymers. (*See* D.I. 157 at 15; D.I. 249 at 69-70; D.I. 160 ¶ 35.) The intrinsic evidence tends to

support Plaintiffs on this point. Specifically, in enumerating suitable materials for inclusion in a controlled release matrix, the patent lists "[h]ydrophillic or hydrophobic polymers" as a distinct and separate item from "vegetable oils and waxes." (*See* '887 patent at 3:50-60.) Thus, even if some who are skilled in the art would understand that, in some contexts, "vegetable oils" are polymers, the patent indicates the possibility of non-polymeric vegetable oil based matrices. Accordingly, even if Defendants actually intended for their definition of "matrix" to cover only "controlled release" matrices, it would still be too narrow by virtue of it being limited to polymeric structures. Furthermore, if I were satisfied that the patents-in-suit set forth only polymers as exemplary materials to incorporate in a "matrix," I still would avoid limiting the scope of the claims based on nothing more than the absence of a more explicit reference to a non-polymeric matrix. *See Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 906 (Fed. Cir. 2004) (requiring "explicit disclaimer" not just the "mere absence of any reference to [a] structure in the specification" to limit claim claim scope); *LG Philips LCD Co. v. Tatung Co.*, No. 04-343-JJF, 2007 U.S. Dist. LEXIS 43557, at *24-*25 (D. Del. June 15, 2007) ("The mere absence of a description of alternative embodiments in the common specification such as a flat screen monitor does not ... rise to the level of words of manifest exclusion or restriction.") (citations omitted).

Finding no adequate reason to limit the term "matrix" to "polymeric" structures that provide drug release through "diffusion" or "erosion," I conclude, as Plaintiffs

contend, that the term "matrix" means a "pharmaceutical preparation that incorporates the active ingredient dispersed within a solid dosage form."

G. "normal release matrix"

Defendants contend that a "normal release matrix" is a matrix that "does not slow the release of the active ingredient." (D.I. 161 at 20.) Plaintiffs offer a similar construction, contending that a "normal release matrix" "does not substantially slow the release of the active ingredient." (D.I. 157 at 17 (emphasis removed).) Thus, the dispute over the meaning of the term appears to be a subtle disagreement as to the precise rate at which the matrix controls drug release. In any event, at the *Markman* hearing, both parties agreed that a "normal release matrix" releases the active ingredient as quickly as feasible. (*See* D.I. 249 at 83-84.) I shall thus construe the term "normal release matrix" to be "a matrix that releases the active ingredient as quickly as feasible."

V. CONCLUSION

Accordingly, for the foregoing reasons, the disputed claim terms will be construed as follows:

	Claim Term	The Court's Construction
1.	"therapeutic effect"	"an effective treatment for pain"

2.	"A [solid] controlled release oral [dosage form/pharmaceutical preparation/pharmaceutical tablet] ... said [dosage form/pharmaceutical preparation/pharmaceutical tablet] providing a therapeutic effect for [at least] about 24 hours"	"a single tablet, not including additional or previously administered tablets, that provides a therapeutic effect for [at least] about 24 hours"
3.	"therapeutic effect for about 24 hours after oral administration"	"an effective treatment of pain for about 24 hours from when the treatment begins to provide its intended effect"
4.	"therapeutic effect for at least about 24 hours"	"an effective treatment for pain for about 24 hours, or longer, from when the treatment begins to provide its intended effect"
5.	"a pharmaceutically effective amount of tramadol or a salt thereof"	"an amount of tramadol or its salt sufficient to achieve a therapeutic effect"
6.	"matrix"	"pharmaceutical preparation that incorporates the active ingredient dispersed within a solid dosage form"
7.	"normal release matrix"	"a matrix that releases the active ingredient as quickly as feasible"

November 4, 2008
Wilmington, Delaware